Published in final edited form as:
Curr Opin Neurol. 2009 August ; 22(4): 340–347. doi:10.1097/WCO.0b013e32832d93dd.

Human Brain Networks in Health and Disease

Danielle S. Bassett[1,2,3] and **Edward T. Bullmore**[2,4]

[1]Behavioral & Clinical Neurosciences Institute, University of Cambridge, Department of Psychiatry, Addenbrooke's Hospital, Cambridge UK

[2]Biological Soft Systems Sector, Department of Physics, University of Cambridge, Cambridge UK

[3]Genes Cognition & Psychosis Program, Clinical Brain Disorders Branch, National Institute of Mental Health, NIH, Bethesda, MD, USA

[4]Clinical Unit Cambridge, GlaxoSmithKline, Addenbrooke's Hospital, Cambridge UK

Abstract

Purpose of review—Recent developments in the statistical physics of complex networks have been translated to neuroimaging data in an effort to enhance our understanding of human brain structural and functional networks. This review focuses on studies using graph theoretical measures applied to structural MRI, diffusion MRI, functional MRI, electroencephalography and magnetoencephalography data.

Recent findings—Complex network properties have been identified with some consistency in all modalities of neuroimaging data and over a range of spatial and time scales. Conserved properties include small-worldness, high efficiency of information transfer for low wiring cost, modularity, and the existence of network hubs. Structural and functional network metrics have been found to be heritable and to change with normal aging. Clinical studies, principally in Alzheimer's disease and schizophrenia, have identified abnormalities of network configuration in patients. Future work will likely involve efforts to synthesize structural and functional networks in integrated models and to explore the inter-dependence of network configuration and cognitive performance.

Summary—Graph theoretical analysis of neuroimaging data is growing rapidly and could potentially provide a relatively simple but powerful quantitative framework to describe and compare whole human brain structural and functional networks under diverse experimental and clinical conditions.

Keywords

network; graph; small-world; modularity; wiring cost

Introduction

The concept of networks in neurology originated in the latter half of the 19th century with the advent of the "disconnection syndromes" hypothesis propounded by Wernicke, Lichtheim, Liepmann, Dejerine and others mainly on the basis of clinico-pathological correlations. The concept was fostered by two developments in related fields: 1) the movement from a

Correspondence and requests for materials should be addressed to E.T.B. (etb23@cam.ac.uk).

characterization of human brain surface morphology towards a direct description of neuroanatomical projection pathways in the white matter and 2) the widespread acceptance of "associationistic" models of cognitive function described by James and Freud [1]. However, the early "diagram-makers", as they were called by their detractors, lost ground to competing theories of brain organization (such as mass action) in the mid-20th century. The central concept of a brain network constructed to segregate and integrate information processing was not again influential until reintroduced to the English speaking world by Norman Geschwind in the 1960s [2,3]. While Geschwind's legacy encouraged deeper exploration into cortico-cortical connectivity organization, noninvasive imaging techniques to probe these relationships in vivo were not yet widely available.

In the past few decades, a plethora of multiscale noninvasive structural and functional neuroimaging techniques have become cost-effective while the basic data preprocessing methods for these techniques have become more finely tuned. Simultaneously, developments within the realm of statistical physics have led to the formation of a new interdisciplinary field, now known as "complex network science", which provides mathematical and conceptual tools for understanding the organization and emergent behaviors of a diverse range of complex real-life networks; see [4] for an accessible introduction and [5] for a comprehensive review of the technical background. A basic insight to have emerged already from complex network science is that substantively different systems can share key organizational principles in common. Moreover, within a complex system like the brain, which exists on many different scales of space and time, it seems that network properties can be highly conserved or scale-invariant. For example, both microscopic cellular networks and macroscopic networks derived from neuroimaging data can demonstrate isomorphic properties such as modularity, the existence of hub nodes, and high efficiency of information transfer for nearly minimal wiring costs; see [6,7] for recent reviews of complex networks in relation to neuroscience generally. In this article we will focus specifically on recent studies using mathematical tools drawn mainly from graph theory to elucidate the complex network properties of the human brain in health and disease.

Graph theoretical concepts for network analysis

In graph theory, a network is reduced to an abstract description as a set of nodes connected by edges (or lines); see Figure 1. The edges can be directed or undirected, and weighted or unweighted. Most graph theoretical analysis of brain networks to date has considered the simplest case of an undirected, unweighted graph.

The nodes and edges of a brain graph can be empirically defined in many ways. For networks constructed from microscopic data, such as studies on the nematode worm Caenorhabditis elegans [8], the nodes would naturally be neurons and the edges would represent the axons connecting neurons to each other. On the other hand, to construct human brain networks at the macroscopic scale of neuroimaging data, we might specify that the nodes were the major subcortical nuclei and cortical regions and the edges represented some statistical measure of association, e.g., correlation or mutual information, between regions [9,10]; see Figure 2.

Once the network has been rendered in graphical form, its topological properties can be measured. A key topological metric is the degree of each node, which is simply the number of edges connecting it to the rest of the network. The probability distribution of degree over all nodes in the network is called the degree distribution and often has a more-or-less truncated power law form compatible with the existence of high degree nodes or network hubs.

Another key metric is the path length which is the number of edges that must be traversed to go from one node to any other node; for a pair of nodes that are nearest neighbors the path length is 1; the average path length over all possible pairs of nodes, sometimes called the

characteristic path length, is inversely related to the global efficiency of the network for parallel information transfer [11]. The clustering coefficient is a measure of the density of connections between nearest neighbors of an index node: high clustering coefficients indicate nodes that are part of a clique of densely inter-connected neighbors. These and other metrics on brain networks can be compared to their values in benchmark networks, such as random networks (which have low clustering and short path length) or regular lattices (which have high clustering and long path length).

Watts and Strogatz, in their highly influential article in 1998 [12], used a simple computational model to show that between the limiting cases of a regular lattice and a random network there exists an intermediate regime of networks characterized by the combination of high clustering and short path length. They called this class of networks "small world", based on previous observations from sociology that social networks often have similar properties of high clustering or cliquishness of relationships in local neighborhoods, combined with a surprisingly short chain of intermediate acquaintances between any two people selected at random from a large population. This analysis has proven to be attractive to systems neuroscientists because it resolves a long-standing tension between localized and distributed models of brain organization: in principle, a small-world network can provide a topological substrate for both locally specialized or segregated processing in neighborhoods of highly clustered nodes, and globally distributed or integrated processing on a highly efficient network with short characteristic path length [13]. Recent work has considerably extended the range of metrics that have been drawn from complex networks science to applications in neuroscience and neuroimaging; see Table 1.

Structural brain networks

Human brain structural networks have been constructed in two ways: either indirectly from inter-regional covariation of gray matter volume or thickness measurements in structural magnetic resonance imaging data, sMRI; or more directly from measurements of white matter connections between gray matter regions provided by diffusion tensor imaging, DTI (or related techniques). Nodes of structural networks have usually been defined as regions of a predetermined anatomical parcellation scheme, such as the automated anatomical labeling (AAL) template image, which divides the cortex into approximate Brodmann areas [18]. To make gray matter networks, based on sMRI data, the edges between nodes are defined by the strength of correlation between regional volume or cortical thickness measurements [42]. For example, in a sample of say 100 people, if there is a strong correlation between cortical thickness in right and left middle frontal gyrus, an edge would be drawn between these nodes in an undirected graph representing the sample mean network. The main advantage of white matter networks, based on DTI, is that techniques such as probabilistic tractography can be used to assign a connection probability between any pair of regional nodes in a single subject.

Moreover, anatomical networks based on tractography in a single subject may seem more straightforwardly related to axonal projections between regions than networks based on inter-regional covariation of gray matter (although see Lerch et al [43] for cross-validation of these two approaches). However, one currently challenging issue for DTI-based networks is that most tractography techniques under-estimate the probability of connections between regions widely separated in space, leading to a relative sparsity of long distance edges in the resulting networks.

Gray matter networks

Gray matter networks in healthy volunteers have been shown to have small-world topology and relatively low wiring costs, i.e., the mean physical distance between connected nodes is considerably less than in a comparable random network, consistent with prior evidence that

nervous systems are organized to nearly minimize wiring costs [14,15]. In normal multimodal cortical networks, a hierarchical organization was demonstrated, with the highest degree nodes having low clustering; transmodal and unimodal cortical networks were less hierarchically organized, suggesting that different cortical divisions might have developed according to different growth rules [14]. There have also been studies of the modular organization of gray matter networks, showing that these can be decomposed into a community of sparsely inter-connected modules, each of which comprises a number of densely intra-connected brain regions [16]. The modular organization of human brain structural networks seems to reflect known functional specializations of the brain regions and is comparable to the modularity of functional networks derived from fMRI [10,21]. A twin design has been used to determine a network of regional structural associations which are under robust genetic control [17], as also validated in functional networks [37].

A study of people with schizophrenia found that their gray matter network was characterized by an increased physical distance between connected nodes, suggestive of inefficient wiring, and attenuated hierarchical organization of heteromodal cortex, which might be indicative of abnormal neurodevelopment [14]. In Alzheimer's disease, gray matter networks have been associated with changes in the degree distribution associated with a more lattice-like network which is highly sensitive to computationally simulated lesions to the hub nodes [15,44].

White matter networks

Three diffusion-based methods have been used in important studies recently to construct white matter networks: diffusion tensor imaging (DTI) [18], diffusion spectrum imaging (DSI) [19], and diffusion weighted magnetic resonance imaging (DW-MRI) [20]. Convergently, these studies suggest that there exists a core of the white matter network which densely interconnects the posterior and medial cortical regions [19], association cortical hubs [20], and has longer-range white matter connections to the rest of the brain [18].

Functional brain networks

Functional brain networks have been constructed from functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG).

fMRI

Functional MR imaging has coarse time resolution (order of seconds) but good spatial resolution (millimeters). It has therefore been used to make anatomically precise, even voxel level [26,28], maps of functional networks operating at low frequencies (< 0.5 Hz).

Two studies this year have confirmed the modular [21] and, in fact, hierarchically modular [22] community structure of healthy functional networks. Meunier et al.(2009) further studied the effect of aging on modular structure, finding an increased number of smaller modules and fewer inter-modular connections to frontal regions in the older adults (mean age = 67.3 years) than in the younger adults (mean age = 24.3 years) [21].

Several recent studies have described the effects of diseases such as schizophrenia, attention deficit hyperactivity disorder (ADHD), and Alzheimer's disease (AD) on fMRI brain networks. Liu et al. (2008) showed that topological measurements such as clustering and small-worldness were inversely correlated with duration of illness in schizophrenia [23]. Supekar et al. (2008) showed that the clustering coefficient was significantly reduced in patients with Alzheimer's disease, and could be used to distinguished AD participants from the controls with a sensitivity of 72% and specificity of 78% [24]. Interestingly, Buckner et al. further showed that the cortical hubs (nodes with high degree) of the resting state functional network also show high amyloid-β deposition in people with Alzheimer's disease [28]; see Figure 3. Children with ADHD seem

to show the opposite trend, with a significantly increased local efficiency (or clustering) compared to age-matched volunteers, with regional changes in efficiency found especially in prefrontal, temporal, and occipital cortices [25].

EEG and MEG

EEG and MEG data contain information about the brain's electromagnetic activity over a wide range of frequencies (~1 to 100 Hz) with millisecond time resolution but relatively poor spatial resolution (centimeters).

Several studies in aging, schizophrenia, and Alzheimer's disease have found functional networks operating in these higher frequencies which show comparable topological changes to those described in the lower frequency fMRI data. For example, the transition from childhood (8–12 yr) to adulthood (21–26 yr) is suggested by Micheloyannis et al. to be characterized by a reduction of overall connectivity (decreased clustering and increased path length) [29]. Similarly, Stam et al. showed, in an analysis of weighted networks derived from resting state MEG data, that patients with Alzheimer's disease had reduced connectivity as shown by decreased clustering and increased path length [40]. Finally, a comparable decrease in local clustering was found in weighted networks derived from EEG data on patients with schizophrenia studied both under resting conditions [30] and while performing a working memory task [31].

The effects of sleep on functional networks have been described in studies using EEG with a relatively small number of electrodes (12–19), resulting in networks that are roughly an order of magnitude smaller than those considered in fMRI and waking electrophysiological techniques. Ferri et al. (2008) reported that small-worldness became steadily greater through light sleep, slow-wave sleep, and REM sleep in frequency bands less than 15 Hz, indicating a definite reconfiguration which may be related to neural plasticity during sleep [32]. Dimitriadis et al. make the further claim that the topological structure of networks in stages 1, 2, 3, 4, and REM are significantly different and can be clearly distinguished with a high sensitivity and specificity using a data driven clustering algorithm [33]. In addition to studies of healthy subjects, Leistedt et al. analyzed the sleep networks of acutely depressed patients and showed that they were characterized by an increased path length, i.e., a randomization of network topology, which may directly impact the cognitive capacity of the brain during wakefulness [34].

Recent challenges and trends

Given the recent explosion of human brain network papers based on graph theoretical analysis of neuroimaging data, a current challenge to the field is to evaluate the convergence of structural and functional networks measured at different frequency and spatial scales using different techniques. Preliminary evidence suggests anecdotally that there is some degree of isomorphism between gray matter and white matter networks, and between disease-related changes in low and high frequency functional networks derived from fMRI and EEG/MEG data, respectively. However, these issues need to be addressed more rigorously and directly, for example by using computational models [45], to provide a more integrated account of brain network organization [46].

Another emerging issue is that we do not yet understand the impact of different methodological choices at several steps of network generation and analysis on the resultant findings. Studies have used different parcellation schemes [26,27], continuous metrics of association [47], edge weights (continuous or binary) [23,30,38,40], and strategies for thresholding association matrices. Encouragingly, many headline results (e.g., network small-worldness) seem to be

robust to methodological details but, nonetheless, it will be important to develop a more rational basis for choosing between alternative options.

Within the past year, we have also seen an increasing interest in studying how networks change, e.g., over time and in response to task demands. While network dynamics seem to have a persistent or long memory component [39], they can also adjust quickly to behavioral changes or cognitive demands [35]. This adaptivity to changing environmental contingencies may be related to evidence that brain networks are dynamically in a critical state, "on the edge of chaos", which facilitates their rapid reconfiguration in response to altered inputs [48]. The inter-dependence of network organization and behavior has already been studied for several specific tasks [29,31,36,49,50]. Recent papers have described methodological developments which could be relevant to more extensive applications of graph theoretical analysis to task-related functional networks in future [41,51,52].

Conclusion

Graph theoretical analysis of human brain network organization based on neuroimaging data has developed rapidly in the last 1–2 years. The basic concepts and techniques have proven to be generally applicable to all major current modalities of neuroimaging data over a wide range of spatial and frequency scales. Preliminary data have also indicated that structural and functional network measures are heritable, abnormal in clinical disorders, and change in the context of normal aging, collectively suggesting that these metrics are capturing aspects of brain organization that are of substantive neurobiological importance.

Acknowledgments

This research was supported by a Human Brain Project grant from the National Institute of Biomedical Imaging & Bioengineering and the National Institute of Mental Health, and by the Intramural Research Program of the National Institutes of Health, NIMH. D.S.B. was supported by the National Institutes of Health Graduate Partnerships Program. Correspondence and requests for materials should be addressed to E.T.B. (etb23@cam.ac.uk).

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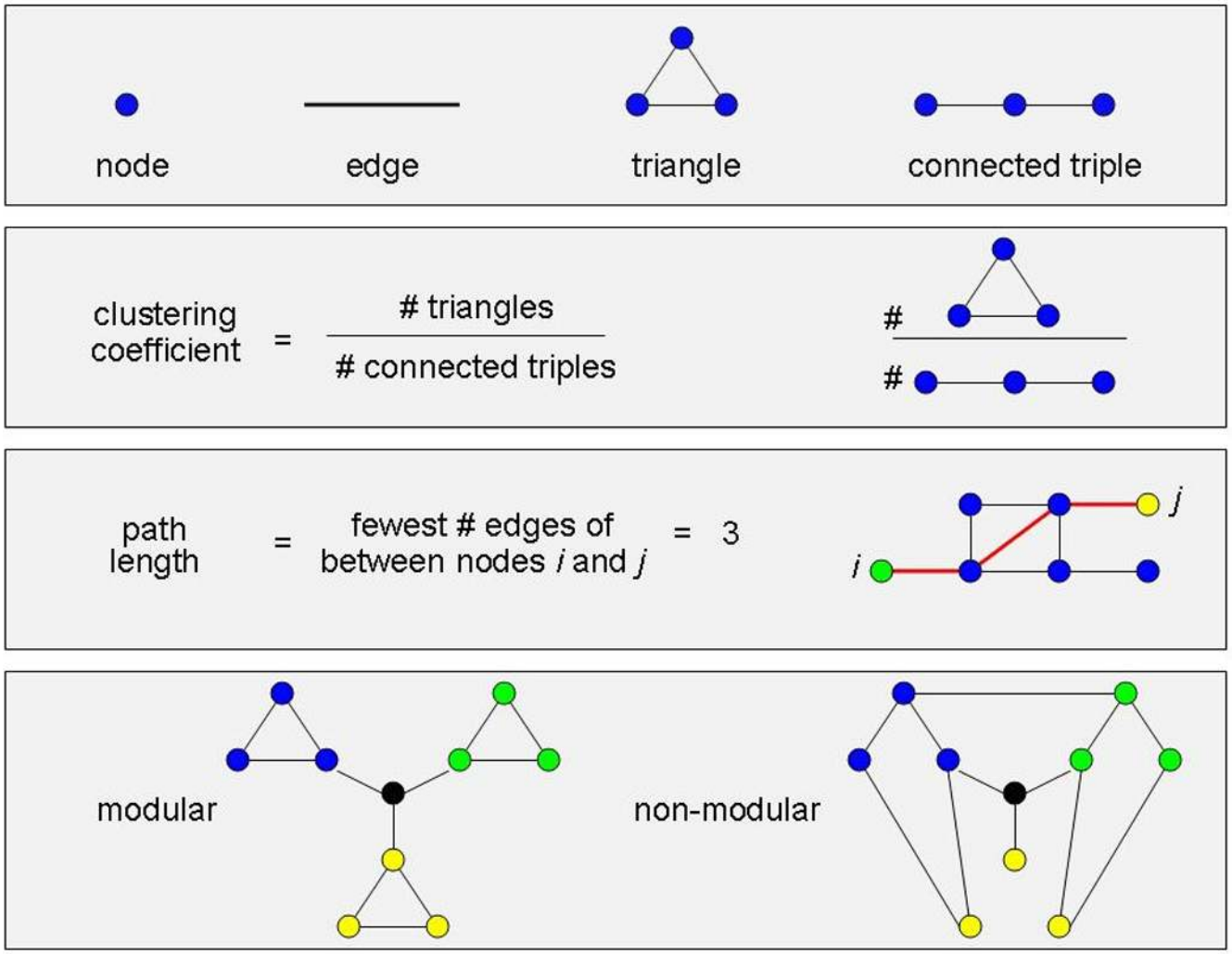

Figure 1.

Tutorial of basic network concepts. *Top Plaque* Definitions for a node, an edge, a triangle, and a connected triple. *Second Plaque* The clustering coefficient, *C*, is given by the ratio of the number of connected triangles to the number of connected triples. *Third Plaque* The path length, *L*, is given by the fewest number of edges linking one node, *i*, to another node, *j*. *Bottom Plaque* A modular network structure occurs when there are more connections within a module than between modules. In this schematic, modules are given by distinct colors, e.g., blue, green, and yellow.

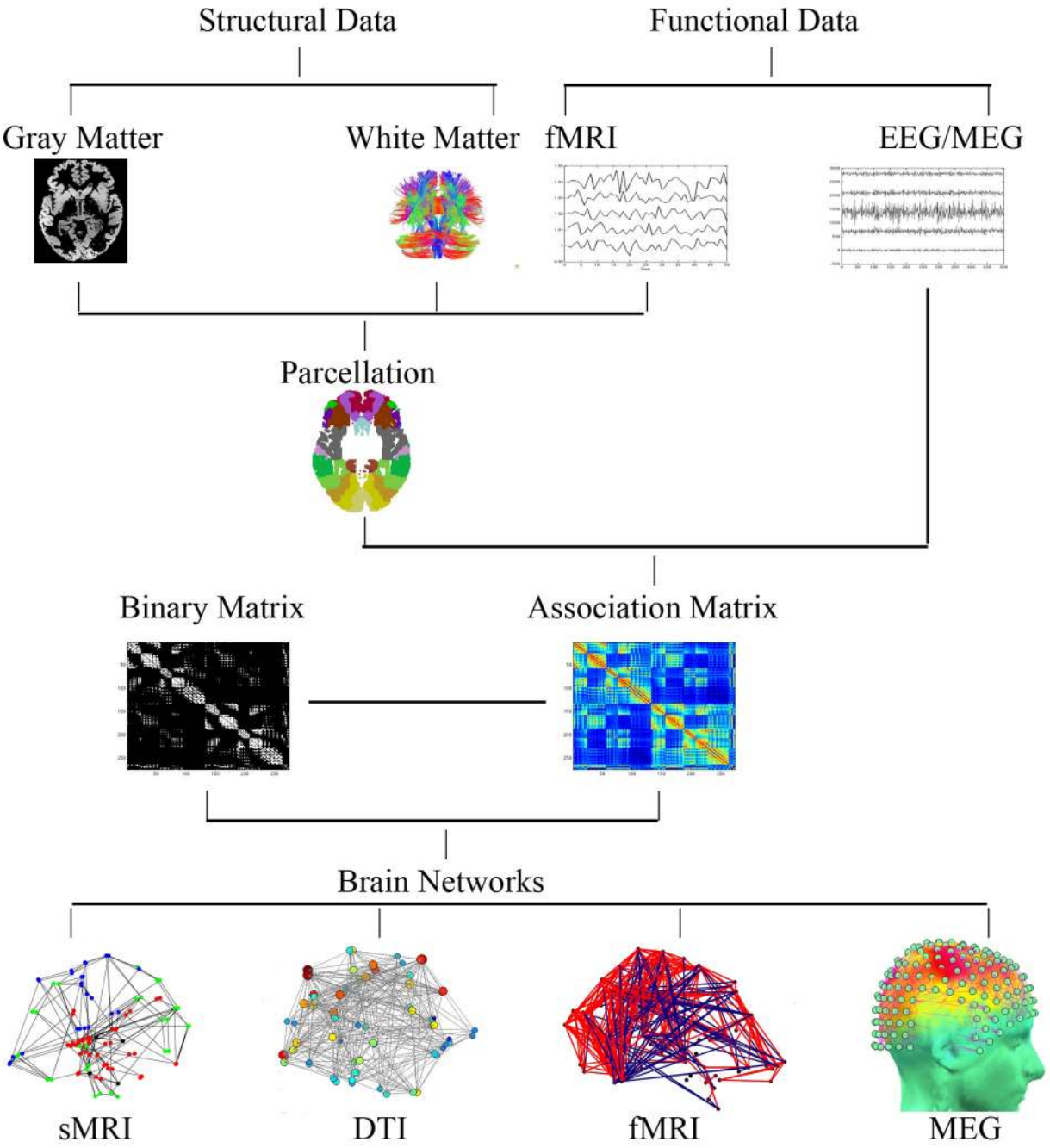

Figure 2.

Workflow of human brain network construction. To construct a brain network, one can begin with either structural (including either gray or white matter measurements) or functional data (including low frequency fMRI data and high frequency EEG or MEG data). Raw data is conventionally put into a parcellation scheme whereby the brain is subdivided into on the order of 100 regions of interest. For EEG and MEG data, this parcellation is already performed by the sensors. The pairwise association between brain regions is then computed, and usually thresholded to create a binary matrix. A brain network is then constructed from nodes (brain regions) and edges (pairwise associations which were larger than the chosen threshold).

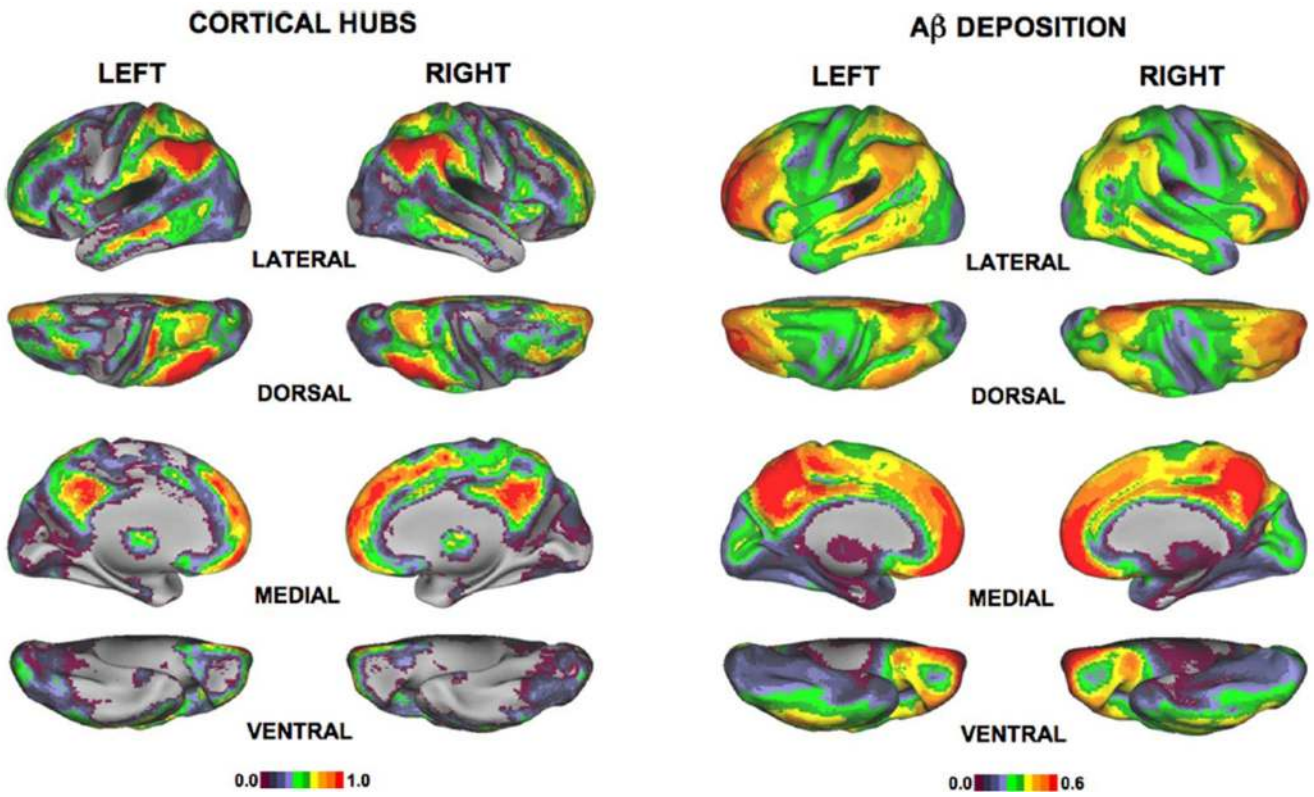

Figure 3.
Network hubs have increased amyloid-β deposition in Alzheimer's disease. *Left* Location of cortical hubs, i.e., nodes with a high number of connections or degree, in healthy resting state fMRI networks. *Right* Location of greatest amyloid-β deposition in people with Alzheimer's disease as measured in a PET study. Reproduced with permission from [28].

Table 1

Methodological details for recent studies

N	Clinical State	Modality	Parcellation	Metric of Association	Edges	Citation
259, 203	Schizophrenia	sMRI, gmv	Brodmann	partial correlation	B	[14]
97, 92	Alzheimer's	sMRI, ct	ANIMAL	correlation	B	[15]
124	None	sMRI, ct	ANIMAL	correlation	B	[16]
600	Twins	sMRI, ct	ANIMAL	correlation	B	[17]
80	None	DW-MRI	AAL	DTI (deterministic)	B	[18]
5	None	DW-MRI	Freesurfer, high-res	DSI	B	[19]
20	None	DW-MRI	AAL	probabilistic tractography	B	[20]
17, 13	Aging	fMRI	AAL	wavelet correlation	B	[21]
53	Resting	fMRI	AAL	partial correlation	B	[22]
31, 31	Schizophrenia	fMRI	AAL	partial correlation	B	[23]
21, 18	Alzheimer's	fMRI	AAL	wavelet correlation	B	[24]
19, 20	ADHD	fMRI	AAL	correlation	B	[25]
18	Resting	fMRI	ANIMAL/AAL	correlation	B	[26]
28	Resting	fMRI	None	correlation	B	[27]
127	Resting	fMRI	None	correlation	B	[28]
20, 20	Aging	EEG	sensors	synchronization likelihood	B	[29]
40, 40	Schizophrenia	EEG	sensors	nonlinear interdependence	W	[30]
20, 20	Schizophrenia	EEG	sensors	coherence	B	[31]
10	Sleep	EEG	sensors	synchronization likelihood	B	[32]
10	Sleep	EEG	sensors	synchronization likelihood	W	[33]
11, 14	Depression	EEG	sensors	synchronization likelihood	B	[34]
5	Movement	EEG	16 ROIs	partial directed coherence	W	[35]
10	Task	EEG	14 ROIs	partial directed coherence	W	[36]
574	Twins	EEG	sensors	synchronization likelihood	B	[37]
11	Seizures	EEG	sensors	synchronization likelihood coherence	B,W	[38]
1	Resting	MEG	sensors	wavelet correlation	B	[39]
18, 18	Alzheimer's	MEG	sensors	phase lag index	W	[40]

N	Clinical State	Modality	Parcellation	Metric of Association	Edges	Citation
2	Task	MEG	sensors	phase-locking value	B	[41]

*Note: B = binary, W = weighted, gmv = gray matter volume, ct = cortical thickness